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Variant of Coffin-Siris Syndrome or Previously Undescribed Syndrome?

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We describe a 23-year-old woman with growth and mental retardation, hypoplasia of the nails and distal phalanges, particularly of the fifth fingers and toes, hirsutism, and a "coarse" face with large mouth and large tongue, and bushy eyebrows. Follow-up from birth to adulthood showed that developmental delay and hypoplasia of nails and distal phalanges are permanent signs. Sparse scalp hair, hypotonia, and feeding difficulties were present in early infancy. Later, growth retardation, hirsutism, and a "coarse" face with midface hypoplasia, broad nose, and large mouth became more impressive.

Differential diagnosis includes a number of conditions, particularly Coffin-Siris syndrome, which is the most likely but not completely convincing diagnosis. Therefore, this woman might represent a variant of Coffin-Siris syndrome or a new entity.

KEY WORDS: Coffin-Siris syndrome, hirsutism, nail hypoplasia

INTRODUCTION

In 1970 Coffin and Siris described a syndrome of growth and mental retardation, brachydactyly of the fifth digits with absence of the nails, lax joints, sparse scalp hair in early infancy and hirsutism later in life, and a "coarse" face characterized by bushy eyebrows, a wide mouth, and thick lips. So far, more than 60 cases have been described [Bartsocas and Tsiantos, 1970; Weiswasser, 1973; Mastroiacovo et al., 1977; Barber and Say, 1978; Carey and Hall, 1978; Gellis and Feingold, 1978; Tunessen et al., 1978; Schinzel, 1979; Giovannucci Uzielli et al., 1980; D'Elia et al., 1981; Lucaya et al., 1981; Mattei et al., 1981; Foasso et al., 1983; Haspeslagh et al., 1984; MacDonald et al., 1984; DeBassio et al., 1985; Palotta, 1985; Bodurtha et al., 1986; Botschkow et al., 1986; Franceschini et al., 1986; Meinecke et al., 1986; Richieri-Costa et al., 1986; Patel et al., 1987; Alembik et al., 1988; Rogers et al., 1988; Burlina et al., 1990; Quazi et al., 1990; Bonneau et al., 1991; Levy and Baraitser, 1991; Rae et al., 1991; De Jong and Nelson, 1992; Quintana-Herrera et al., 1993; van Heyst et al., 1993; Imaizumi et al., 1995; Bonioli et al., 1995; Munson and Perszyk, 1995; Swillen et al., 1995]. Six sets of sibs [Barber et al., 1978; Carey and Hall, 1978; Mattei et al., 1981; Haspeslagh et al., 1984; Franceschini et al., 1986; Rabe et al., 1991] and parental consanguinity in two families [Giovannucci Uzielli et al., 1980; Richieri-Costa et al., 1986] suggest autosomal recessive inheritance. However, the female preponderance of 4:1 is unusual for an autosomal recessive disorder.

Here, we report on a 23-year-old woman with many manifestations of Coffin-Siris syndrome, except for normal occipital circumference, midface hypoplasia, and a slightly different hand pattern profile, particularly of the metacarpals.

CLINICAL REPORT

The female patient was born at term after an uneventful pregnancy. No exposure to drugs or radiation was reported. The mother was 32 years old and the father 31. Both parents and three older sibs are healthy. Family history is unremarkable. There is no parental consanguinity.

A placenta previa required cesarean section. Prenatal infections were excluded. Birth weight (2,500 g) and length (49 cm) were between the 10th and 50th centile. Occipitofrontal circumference (OFC) is not known.

At 14 months length (71 cm), weight (8 kg), and OFC (44 cm) were below the 3rd centile. Poor suck, brachycephaly with sparse scalp hair, small nails, short hands and feet, generalized hypotonia, and striking developmental delay were noted. Sitting was not possible; head control was achieved in the prone position only. Perinatal asphyxia was assumed.

Dermatoglyphics of the fingertips were U,U,U,U,A on the right and U,R,U,U,U on the left; total finger ridge count 93; 9·7·5·2-t·L^r·0·0·0·L on the right palm and 9·7·5·1·t·L^r/L^u·0·0·0·L on the left palm. Dermato-

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glyphics of the toes were as follows: W,-,F,-,F on the right and W,-,-,-,F on the left; $L^d{\cdot}0{\cdot}L^d{\cdot}0{\cdot}L^t$ on the right sole and $L^d/L^t{\cdot}0{\cdot}0{\cdot}0{\cdot}0$ on the left sole.

Her face was characterized by midface hypoplasia, a broad nasal bridge, and a large tongue (Fig. 1a,b). Hypothyroidism and other metabolic disorders were excluded by routine methods. Karyotyping at a level of 500 bands, echoencephalography, and electroencephalography gave normal results. Bone age was strongly retarded (Fig. 2a), and hand pattern profile (Fig. 2b) displayed short metacarpals and phalanges, particularly of the middle and distal phalanx of the fifth finger. Metacarpals were less affected.

At the age of 23 years height (150 cm) was below the 3rd centile, whereas OFC (54 cm) was between the 25th and 50th centile. Eye measurements were as follows: outer canthal distance (100 mm) above the 97th centile, interpupillary distance (65 mm) on the 97th centile,

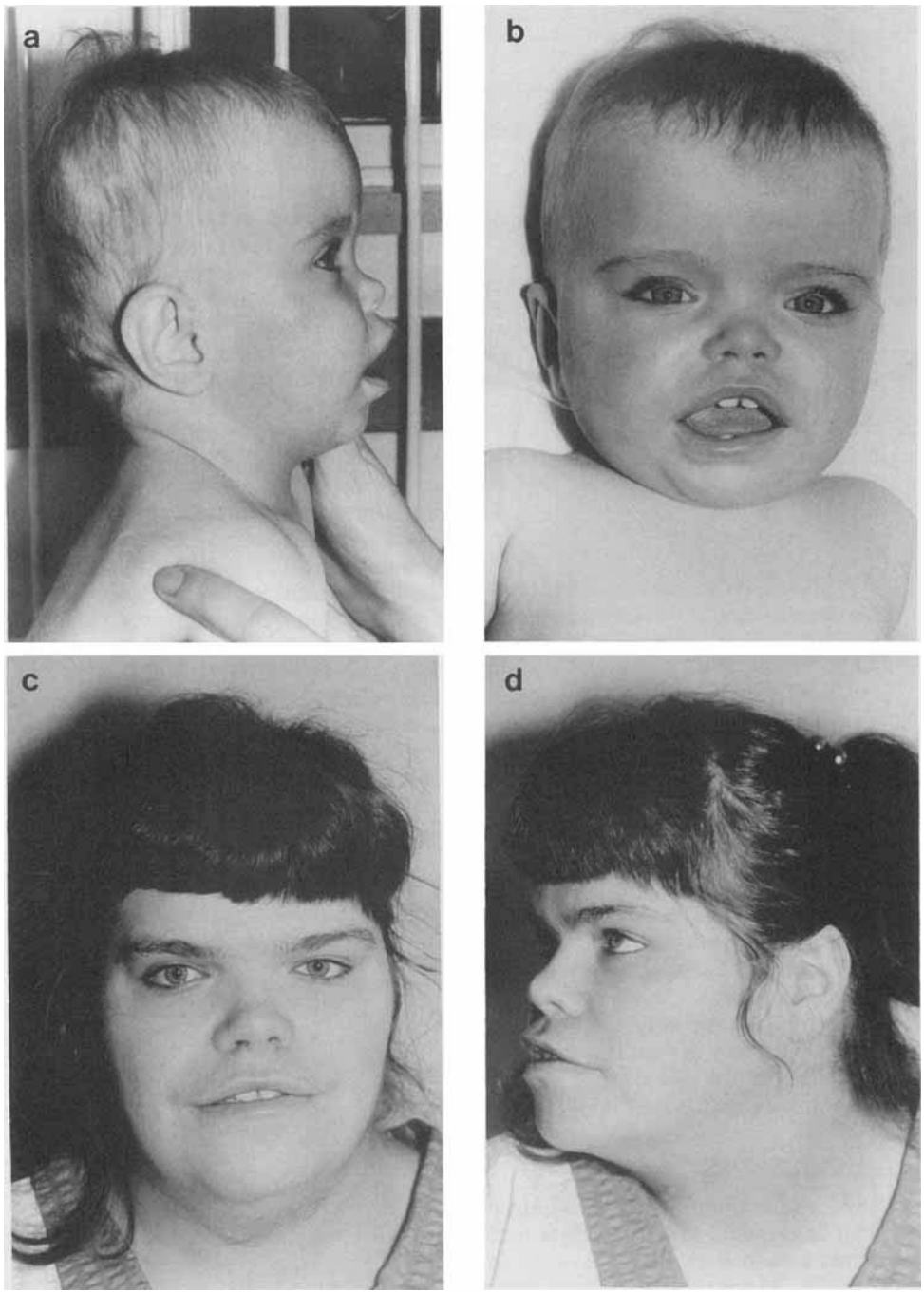

Fig. 1. The patient at 14 months **(a,b)** and 23 years **(c,d)**. A wide mouth, a broad nose, bushy eyebrows, and thick lips are present at both ages, but more impressive at a later age. Scalp hair is sparse in infancy. Later in life hirsutism and dense scalp hair is found.

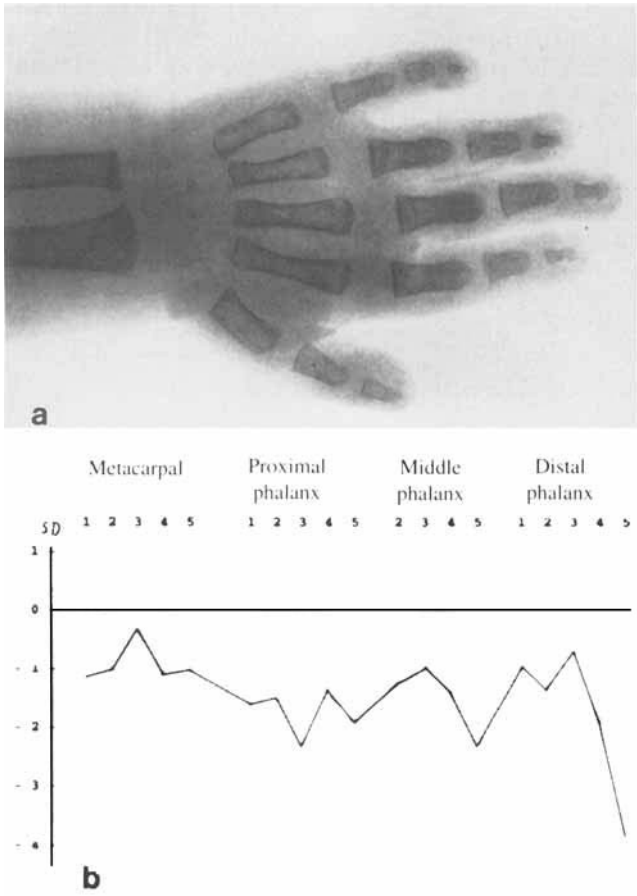

Fig. 2. X-ray **(a)** and hand pattern profile **(b)** of the right hand at 14 months. Length of metacarpals and all phalanges is reduced, but shortness of middle and distal phalanges of the fifth finger is most impressive.

and inner canthal distance (35 mm) below the 97th centile, respectively. The woman was able to form short sentences and to answer simple questions. Nevertheless, moderate mental retardation was obvious. She still had hirsutism, small palpebral fissures, midface hypoplasia, a broad nose, a large tongue, and a wide mouth (Fig. 1c,d). Body and limbs also were hirsute. Scalp hair was dense and hairline on the back was low. Patellae were small. There was no kyphoscoliosis and no joint laxity. Sexual development was normal. Hands and feet were short with hypoplastic nails and terminal phalanges (Fig. 3). Total hand length was 15.5 cm, total foot length 21 cm, both below the 3rd centile. Middle finger length (6.5 cm) was on the 3rd centile.

DISCUSSION

Hypoplasia of the nails and distal phalanges, particularly of the fifth fingers and toes, is a major finding in our patient, but also occurs in more than 70 syndromes listed in POSSUM version 4.0 [1994]. If the additional manifestations of our patient are considered, differential diagnosis is restricted to several chromosomal aberrations, particularly trisomy 9p, the autosomal dominant nail-patella syndrome, hydantoin syndrome, Brachmann de Lange syndrome, Coffin-Lowry syndrome, brachymorphism-onychodysplasia-dysphalangism syndrome, Coffin-Siris syndrome, and DOOR(S) syndrome. The latter can be excluded by the presence of deafness, triphalangeal thumbs, and seizures [Hess and Pecote, 1984]. Karyotyping ruled out trisomy 9p [Smart et al., 1988; Schinzel, 1994]. Nail-patella syndrome is additionally characterized by dystrophic and hypoplastic nails and hypoplasia of capitellum/radial head and patella/lateral femoral condyle, respectively [Rizzo et al., 1993]. Mental retardation is rare and no characteristic face has been described. Hydantoin syndrome can be excluded by a careful anamnesis regarding any drug intake during pregnancy [Hanson, 1986]. Brachmann de Lange syndrome is likely, if synophrys and flared nostrils in association with micromelia/oligodactyly and any heart defect are found [Jackson et al., 1993]. Brachymorphism-onychodysplasia-dysphalangism syndrome patients have microcephaly, different facial changes, and only slight mental impairment [Verloes et al., 1993]. Female carriers of the X-linked dominantly inherited Coffin-Lowry syndrome have neither sparse scalp hair in early infancy, nor hirsutism, hypoplasia of the nails and distal phalanges, particularly of the fifth fingers, small patellae, or bushy eyebrows [Young, 1988].

Frequent findings in patients with Coffin-Siris syndrome are hypoplasia or absence of the nails and distal phalanges, particularly of the fifth fingers and toes, small patellae, mental retardation, sparse scalp hair, hirsutism, and an unusual face, as described in our patient. A careful review of published cases with Coffin-Siris syndrome demonstrates variable expression, but also makes the diagnosis in some of them uncertain. If there is a lack of typical findings such as sparse scalp hair in infancy, hirsutism, or a "coarse" face with a wide mouth and thick lips, as in several reported cases [Barber et al., 1978; Ueda et al., 1980; Mace et al., 1973], Coffin-Siris syndrome is rather unlikely.

Moreover, Coffin-Siris syndrome is an excellent instance of an age-dependent phenotype, as is obvious in

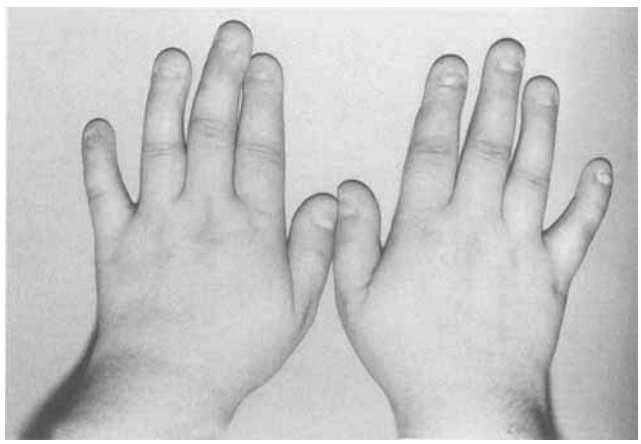

Fig. 3. Short hands and fingers with hypoplasia of the nails and distal phalanges, particularly of the fifth fingers at the age of 23 years.

our patient. Developmental delay, hypoplasia of nails and distal phalanges, particularly of the fifth fingers and toes, are age-independent findings. Sparse scalp hair, feeding difficulties, and muscular hypotonia are typical manifestations in infancy. Later in life, scalp hair is denser and hirsutism, microcephaly, growth retardation and facial changes including a broad nose, wide mouth, and thick lips become more evident.

Our patient has a normal head circumference, so far described in only four cases with Coffin-Siris syndrome [Bartsocas and Tsiantos, 1970; Foasso et al., 1983; Mace and Gotlin, 1984; De Jong and Nelson, 1992], milder mental retardation, relatively long metacarpals, and midface hypoplasia. Thus a certain diagnosis is not possible in our patient.

Hypoplasia of the nails and distal phalanges, particularly of the fifth fingers and toes, hirsutism, growth and mental retardation, and some of the facial findings point to Coffin-Siris syndrome. Normal head circumference, midface hypoplasia, and relatively long metacarpals are rare in Coffin-Siris syndrome. Thus our patient may represent a variant of Coffin-Siris syndrome or a new entity. We hope that the present report will encourage publication of similar cases and, moreover, might help to delineate the phenotype of Coffin-Siris syndrome.

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